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PREMATURE BEATS AND EXTRASYSTOLES*

Premature contractions of the cardiac chambers occur in a variety of conditions. Thus, an ectopic pacemaker, protected by an unknown mechanism from the prevailing basic rhythm, may be responsible, as in parasystole; a faster A-V rhythm may interfere with a protected sinus rhythm, as in dissociation with interference. Premature beats are a feature of flutter, in many instances, and are always present in atrial fibrillation. The present discussion will be restricted to the most frequent form of premature contractions presenting a constant coupling to the existing basic rhythm. It is this form of premature contractions which we call extrasystoles and it is generally agreed that the beat preceding the extrasystole plays a role in its production, although the mechanism is still unknown.

The study of extrasystoles is fascinating. At one end of the scale they may be asymptomatic; at the other they may cause great distress. They can constitute a harmless, insignificant anomaly or a single extrasystole may cause ventricular fibrillation and sudden death. Since antiquity, patients and physicians have been alarmed by them.

Significance

It is unlikely that any individual would go through life without ever having had an extrasystole. Although more than half the cases of extrasystoles which come to the attention of the physician are without significance, in many instances they arise from a pathological myocardium and sometimes constitute the only and earliest sign of disease. Their appearance after exertion may be the earliest and only objective sign of coronary sclerosis. In diphtheria, they may be the first evidence of myocardial involvement. They are common in myocardial infarction. For reasons unknown they are relatively uncommon in myocarditis caused by rheumatic fever, cocci, and viruses. They are often encountered in pregnancy. They tend to be more prevalent at rest (slow rate) and to disappear after exercise. They may appear even in the healthy only after exertion. The latter, however, is unusual.

Varieties of Extrasystoles

Extrasystoles may originate in any part of the heart, but rarely in the sinus node or the bundle of His. Only uncommonly do they originate in the A-V node, although this diagnosis is often (and mistakenly) made. It is noteworthy that the centers with the greatest capacity for automatic, spontaneous impulse formation rarely give rise to extrasystoles. Most extrasystoles presumably arise in peripheral twigs of the sinus node, in the atrial portion of the A-V node or in the ramifications of the conduction system in the ventricles. Whether extrasystoles spring from the myocardial fibers is not decided; recent investigations suggest they do. It is not established whether atrial or ventricular extrasystoles are the more frequent. Extrasystoles occur often in A-V block, particularly when there is bilateral bundle branch block. Presumably the process which leads to the block is also responsible for the formation of ectopic impulses.

Of great interest are the so-called "return extrasystoles." A ventricular extrasystole is conducted in a retrograde manner to the atria and returns in some area of the A-V conduction system, reactivating the ventricles. Closely related are the extrasystoles which appear during an A-V rhythm in which the atria are activated much later than the ventricles. Here, too, the impulse is returned from the atria to the ventricles so that the latter are activated a second time from a single ectopic impulse. These extrasystoles are rare in man.

There are all gradations in the frequency of extrasystoles. They may be single, occur after every normal beat, appear in runs of two, three or any number, or may lead finally, without any sharp boundary, into paroxysmal tachycardia. Clinically very important are variform extra-

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systoles, for they always signify myocardial pathology. Their form may vary because a single focus has variable aberrant conduction, or because there are several foci of origin. Rare in man, but common in animal experiments, are "extrasystoles in groups," that is, two or more extrasystoles separated from similar groups by a longer pause.

It can be determined whether an extrasystole arises from the atria or ventricles as well as the general location within these chambers. Thus one can in a general way, by defining the mean vector of the extrasystoles, find out whether the origin is left, right, anterior, posterior, superior or inferior. This is valid only if the conduction of the impulse is uniform in all directions from the focus out.

Symptoms

Much uncertainty exists regarding the incidence and mechanism of symptoms. Most extrasystoles are asymptomatic. In some, the sensations accompanying them are very unpleasant, even terrifying. Particularly is this so in conditions in which the stroke volume tends to be large, as in aortic insufficiency. It is not known why the sensation of standstill of the heart is experienced, since the postextrasystolic pause is certainly too short to create this feeling. Nor is it understood why some patients suffer from a brief knife-like pain with each extrasystole. The sudden jumping, bolting, twisting, and other similar sensations are most often felt with the first postextrasystolic beat and are explained by its larger stroke volume. Patients with Wenckebach periods never experience such symptoms for reasons unknown, even though the pause created by the dropped beat is often longer. A remarkable phenomenon, and in our experience not uncommon, is an involuntary cough appearing simultaneously with each extrasystole. It appears to be an example of an autonomic reflex originating in the heart. Its mechanism is not clear.

Differential Diagnosis

Usually extrasystoles are readily recognized without but more easily and more often with the electrocardiogram. Mistakes are not infrequent. Parasystole and dissociation with interference are often diagnosed mistakenly as extrasystoles even with an electrocardiogram available. It is difficult to make a clinical diagnosis when only occasional extrasystoles occur in atrial fibrillation. Flutter with an alternating 4:1 and 2:1 block may be confused with a bigeminal extrasystolic rhythm. Especially, without a tracing multiple ventricular extrasystoles may be labeled atrial fibrillation. Most serious is the assumption of the presence of atrial fibrillation with a rapid ventricular rate when actually atrial or ventricular tachycardia exists with an irregular rate as a result of digitalis administration. If then, larger digitalis doses are given before the true nature of the arrhythmia is recognized, the result may be fatal.

Drugs and Extrasystoles

Those caused by caffeine and nicotine are well known, but rare. Less familiar, but more important, are the extrasystoles (and tachycardias and fibrillation) which follow adrenalin and other pressor amines. One of the best investigated forms is that seen during chloroform inhalation. Here the extrasystoles are so common and dangerous that their occurrence has been the chief reason for abandoning this type of anesthesia. Cyclopropane also induces extrasystoles, but the mechanism is not yet defined. Many other substances elicit extrasystoles, even those used to suppress them, such as quinidine and procaine. The most common drug-induced form is the digitalis extrasystole.

Digitalis often causes a bigeminal rhythm consisting of an extrasystole following each dominant beat. It may appear suddenly, although usually it is preceded by solitary, occasional extrasystoles. Digitalis extrasystoles are almost exclusively ventricular; characteristically they are multiform, but sometimes the tracing has to be scrutinized carefully to find the varying form. Especially ominous are multiple extrasystoles whose QRS complexes in a given lead alternate positively and negatively. These indicate dangerous toxicity.

It is remarkable that large, lethal doses of digitalis do not cause extrasystoles (except terminally) when the heart is otherwise healthy and in most heart patients large doses do not cause extrasystoles. On the other hand, some cardiac patients develop dangerous extrasystoles after taking an average maintenance dose for only a few days. It is now known that extrasystoles are especially likely to occur in patients who have been depleted of potassium. This occurs in prolonged congestive failure where the chronic anoxia causes a marked loss of intracellular potassium. Other causes of potassium loss are diuretic therapy (Diuril!), diarrhea, and potassium-losing kidney disease.

If, during the exhibition of digitalis, extrasystoles appear *de novo* or increase in frequency, and especially if they are multiform, the drug must be stopped. Potassium and, in some cases, quinidine must be given. If congestive failure persists, a new attempt with digitalis may be made after the arrhythmia has stopped; occasionally the extrasystoles do not reappear. Digitalis extrasystoles may persist for more than three weeks after discontinuing the drug.

It is not safe to continue the digitalis therapy when potassium and quinidine are necessary to suppress the extrasystoles. The administration of the latter drugs, especially at night, may be omitted or delayed, whereupon fatal ventricular fibrillation may appear.

Digitalis rarely, if ever, causes single atrial extrasystoles or atrial bigeminy. It does cause multiple atrial extrasystoles and paroxysmal atrial tachycardia which characteristically have a relatively high degree of A-V block. It is probable that the increase of the vagal tonus caused by digitalis is responsible for the absence of isolated atrial extrasystoles, since local application of digitalis to the atria causes extrasystoles as readily as when applied to the ventricles.

The frequently encountered statement that digitalis causes extrasystoles by increasing the excitability of the heart is incorrect. It diminishes the excitability as measured by threshold and chronaxie methods. The formation of extrasystoles is not a function of excitability, but of other factors.

Acute Myocardial Infarction

In experimental infarction, extrasystoles often develop into ventricular fibrillation; therefore they should be considered as a serious matter in clinical infarction. They usually, but not invariably, disappear promptly when 0.2 Gm. of quinidine sulfate is given every six hours. While there is agreement as to the general indications and efficacy of this therapy, the controversy persists as to whether it is indicated in every acute infarction. We favor such a policy because ventricular fibrillation may follow the first extrasystole or the extrasystoles may increase so quickly in number that any delay in treatment may be fatal. Arguments against this preventive measure are based on a few experimental studies in which the mortality was greater in the animals receiving quinidine immediately before or after coronary artery ligation, as compared to the animals not receiving quinidine. In these experiments, quinidine was given intravenously and in large dosage. It is necessary to repeat these experiments with a dose of quinidine more comparable to clinical use. Clinical data on the prophylactic therapy are encouraging, but here too, more study is required.

Clinical Importance and Prognosis

The propulsive efficiency of the heart is impaired by a single extrasystole directly proportional to its prematurity and shortness of filling period. This is "compensated" by the postextrasystolic pause, so that in most instances even a continuous bigeminal rhythm does not reduce significantly the over-all function. A significant impairment may develop when several extrasystoles follow each other, or in a bigeminal rhythm when each extrasystole is interpolated. Then the cardiac output falls, the blood pressure declines and congestive failure may develop. In patients with coronary artery stenosis, anginal pain may be provoked by a run of extrasystoles. It is caused by the rapid heart rate and consequent poor filling and ejection. The conduction disturbance within the ventricle associated with ventricular extrasystoles appears to have no significant effect on the ventricular efficiency.

Multiform extrasystoles signify myocardial disease; the prognosis will be that of the underlying pathology.

In a diseased myocardium, an extremely early premature extrasystole may elicit ventricular fibrillation. The very end of the absolute refractory phase or the beginning of the relative refractory phase constitute the vulnerable or critical phase when any stimulus, such as an extrasystole (either ventricular or an atrial one which is conducted early to the ventricle) may induce ventricular fibrillation. It is possible that some of the authenticated instances of sudden death in man or animals, caused by fright or anger, are related to this mechanism. Extrasystoles may be provoked by emotion by way of the hypothalamus, sympathetic stimulation and secretion of adrenalin and other pressor amines. One such premature beat arising in the vulnerable phase may lead to ventricular fibrillation.

Therapy

The majority of extrasystoles do not require therapy. Sometimes the fear engendered by them does force us to treat them. Quinidine, digitalis or both are able to abolish most extrasystoles. Of course, digitalis is used only when it is certain that it has not induced the particular arrhythmia. Procaine amide (Pronestyl) may be substituted for quinidine when the patient is sensitive to quinidine.

Extrasystoles should be suppressed in the following states: when digitalis has induced multiple ventricular extrasystoles; in recurrent paroxysmal tachycardia because extrasystoles presage a paroxysm; in acute myocardial infarction; and in mitral stenosis when there are atrial extrasystoles, because they may lead to atrial fibrillation.

Mechanism

All modern theories assume that the extrasystole is induced by the preceding beat; in other words, it is a "forced" beat (Lewis) and not a completely automatic one.

In the re-entry theory now widely held, the excitation wave of the beat preceding the extrasystole does not come to an end after its spread over the heart. Owing to a local disturbance of conduction, it is delayed and proceeds slowly in the depressed region. In the meantime, the rest of the myocardium has recovered from the systole of the initiating beat, so that this slowly moving portion of the excitation wave finds excitable tissue and a new excitation wave spreads from this area over the heart. No proof has been offered that this re-entry mechanism causes the common type of atrial or ventricular extrasystole (nor is there proof of any other theory at pres-

ent). Actually, gross circus movements have been recorded experimentally in muscle rings and similar preparations. Also, clinically they are present in the return extrasystole which has been described above. Here the impulse originates in a ventricle or A-V node, stimulates the ventricles once, is conducted back to the atria and then back again to the ventricles, so that the latter are activated twice by a single impulse. The only experimental basis for the re-entry theory is the frequently quoted experiment of Schmitt and Erlanger on turtle muscle strips. They found that stimulation of end A of the strip leads to spread of excitation to end B and that the impulse then returns immediately back to end A. This was explained by longitudinal dissociation of conduction so that the impulse spreads only in one part of the strip and returns in the other. Newer investigations show that the reappearance of the impulse is better explained by the after-potentials mentioned below (reflected contractions of Bethe, pseudo-reflex of Arvanitaki). This actually supports the other theory, namely, the induction of a new impulse in a circumscribed site.

We favor the theory of the formation of an extrasystolic impulse in a circumscribed focus. The impulse of the pre-extrasystolic beat spreads over the heart and activates all the fibers. Normally the heart would not be activated again until stimulated by the pacemaker. Occasionally, in one fiber (center) another depolarization follows and leads to the spread of a second contraction. The second depolarization is caused by the so-called negative after-potentials, or oscillations; that is, partial depolarizations of the cell membrane which under certain conditions follow the complete depolarization in nerve, skeletal and heart muscle. If this negative after-potential reaches a certain threshold, a complete depolarization follows and leads to a propagated impulse. An excellent means for eliciting local potentials which may be oscillatory is slight decalcification as accomplished by treatment of a part of nerve, skeletal or heart muscle with sodium citrate or oxalate.

During the negative after-potential, the cell is slightly depolarized and therefore more excitable (supernormal phase). It is therefore possible that weak impulses which are not able to elicit a response later in diastole may excite during this phase. This may be an explanation for certain extrasystoles such as those in acute myocardial infarction, where the injury current may be able to cause responses only during the supernormal phase.

If after-potentials arise locally because of local enzyme action, electrolyte disturbances or change of pH, extrasystoles will appear. They are, therefore, not the expression of increased excitability. This conception explains why such a great variety of factors cause or abolish extrasystoles, and seems to us to explain all the known facts better than does the assumption of a focal conduction disturbance and a re-entry mechanism. It does not rule out the existence of the latter mechanism in certain special situations.

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